VERMONT
Office of Vermont Health Access

Therapeutic Class Review
Lipotropics - Bile Acid Sequestrants

I. Overview

Dyslipidemia is a complex of related conditions that affects many individuals. Multiple lipid-lowering agents, or antilipemic agents, are available and have been divided by the American Hospital Formulary Service (AHFS) into the following classes: bile acid sequestrants, cholesterol absorption inhibitors, fibric acid derivatives, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), nicotinic acid (niacin), and omega-3 acid ethyl esters.[1] The bile acid sequestrant class consists of cholestyramine, colesevelam and colestipol of which cholestyramine and colestipol are available generically.[1] Bile acid sequestrants are primarily indicated to reduce total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[2-5]

Cholesterol is a precursor to bile acid. The production and degradation of cholesterol by the liver involves many steps, pathways and biochemicals. Bile acid sequestrants interrupt one step in the cycle. These agents, as anion exchange resins, bind bile acid in the intestine and the complex is excreted in the feces, interrupting the enterohepatic circulation of bile acid.[6] The resultant decrease of bile acid in the liver stimulates the breakdown of cholesterol, lowering overall cholesterol levels. Bile acid sequestrants can lower LDL-C by 15%-30%, in addition to raising high-density lipoprotein cholesterol (HDL-C) by 3%-5%.[7]

The bile acid sequestrants that are included in this review are listed in Table 1. Colesevelam is available as oral tablets; cholestyramine is available as a powder for suspension and in packets containing powder for suspension; colestipol is available as oral tablets as well as granules for oral suspension. This review encompasses all dosage forms and strengths.

Table 1. Bile Acid Sequestrants Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
cholestyramine and aspartame	powder (bulk or packet)	Questran Light®*	cholestyramine light
cholestyramine and sucrose	powder (bulk or packet)	Questran®*	cholestyramine
colesevelam	tablet	Welchol®	none
colestipol	tablet, granule (bulk or packet)	Colestid®*	colestipol

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the bile acid sequestrants are summarized in Table 2. For a comprehensive overview of the treatment of dyslipidemia, please refer to the Appendix.

In January 2008, colesevelam received approval from the Food and Drug Administration (FDA) for the indication of type 2 diabetes, as an adjunctive treatment to diet and exercise to improve glycemic control. The most recent guidelines on the treatment of diabetes mellitus, from the American Diabetes Association, were released in the same month. They do not incorporate colesevelam, or any other bile acid sequestrants, into their treatment algorithm and therefore are not included in Table 2.

Table 2. Treatment Guidelines Using the Bile Acid Sequestrants

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[8]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of heterozygous familial hypercholesterolemia (FH) • Begin LDL-C-lowering drugs in young adulthood. • TLC indicated for all persons. • Statins: first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple-drug therapy (statins and bile acid sequestrants and nicotinic acid). For the treatment of homozygous FH • Bile acid sequestrants are not effective. For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[7]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid.

Clinical Guideline	Recommendation
	Bile Acid Sequestrants • Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL-C, for younger persons with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy, and for persons needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in persons with very high LDL-C levels.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)[9]**	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)[10]**	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)[11]**	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)[12]**	• Statins are considered first-line drugs for lowering LDL-C. • Bile acid sequestrants can serve as effective lipid-lowering alternatives. • Bile acid sequestrants tend to increase triglycerides (TG); should only be used when TG are <~180 mg/dL or given in conjunction with TG-lowering agents. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Association of the Study of Liver Disease (AASLD): **Management of Primary Biliary Cirrhosis (2000)[13]**	• There is no evidence that topical treatments are effective in treating pruritus associated with primary biliary cirrhosis (PBC). • Ursodeoxycholic acid therapy is currently supported by the most data and is recommended for use in appropriately selected patients with PBC, who have abnormal

Clinical Guideline	Recommendation
	liver chemistry. • Pruritus is a complication of PBC and cholestyramine is the drug of choice for the treatment of this complication. • Rifampin is a second-line treatment option for pruritus to those who fail or are intolerant to cholestyramine. • Opioid antagonists and liver transplant are third- and fourth-line options.

III. Indications

Food and Drug Administration (FDA)-approved indications for the bile acid sequestrants are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Bile Acid Sequestrants [2-5]

Drug	Cholestyramine	Colesevelam	Colestipol
For the reduction of elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia (Fredrickson Type IIa, elevated LDL-C)*	✔	✔	✔
In combination with an HMG-CoA reductase inhibitor, for the reduction of elevated serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia (Fredrickson Type IIa), as adjunct to diet and exercise		✔	
For the relief of pruritus associated with partial biliary obstruction	✔		
To improve glycemic control in adults with type 2 diabetes mellitus†		✔	

*As adjunctive therapy to diet, for patients who do not respond adequately to diet
†As adjunctive therapy to diet and exercise

IV. Pharmacokinetics

The pharmacokinetic parameters for the bile acid sequestrants are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Bile Acid Sequestrants [2-5,14,15]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Renal Excretion (%)	Elimination	Half-Life (hours)
Cholestyramine	0	0	None	None	0	Feces 100%	Not reported
Colesevelam	0	0	None	None	0.05	Feces near 100%	Not reported
Colestipol	0	0	None	None	<0.05	Feces 100%	Not reported

V. Drug Interactions

Significant drug interactions observed with the bile acid sequestrants are identified in Table 5. The bile acid sequestrants have the potential to bind to other drugs, which may delay or reduce the absorption of concomitant oral medications.[15] To minimize this interaction, other drugs should be taken at least 1 hour before, or 4-6 hours after the bile acid sequestrants.[3,4] The manufacturer recommends that drugs that interact with colesevelam or those that have not been tested, be taken 4 hours before colesevelam.[5] Monitoring is recommended for drugs that have a narrow therapeutic index or safety range, and are taken with bile acid sequestrants.[2-5] It is worth noting that the NCEP ATP III states that colesevelam does not need to be administered separately from other drugs, because it does not effectively decrease the absorption of drugs given in conjunction with it.[8]

Table 5. Significant Drug-Drug Interactions for the Bile Acid Sequestrants[5,15]

Drugs	Significance Level	Interaction	Mechanism
Bile acid sequestrants (cholestyramine, colestipol)	2	Corticosteroids (hydrocortisone)	Bile acid sequestrants may decrease the gastrointestinal (GI) absorption of hydrocortisone, resulting in lower systemic levels of corticosteroids.
Bile acid sequestrants (cholestyramine, colestipol)	2	Digoxin	Cholestyramine and colestipol may decrease GI absorption of digoxin, as well as alter the enterohepatic recycling of digoxin. This may result in lower systemic levels of digoxin. In addition, administering colestipol with digoxin may result in a shorter half-life of digoxin, potentially decreasing the effectiveness of digoxin.
Bile acid sequestrants (cholestyramine, colestipol)	2	Loop diuretics (furosemide)	Cholestyramine and colestipol may decrease the GI absorption of furosemide, due to binding by the anion exchange resins, resulting in lower systemic effects of furosemide. Cholestyramine and furosemide administration should be separated by as much time as possible (at least 2 hours). Colestipol should be taken as long as possible (at least 2 hours) after furosemide.
Cholestyramine	2	Anticoagulants (dicumarol, warfarin)	Cholestyramine may decrease the GI absorption of oral anticoagulants, resulting in lower systemic levels of anticoagulants, and potentially decreasing the effectiveness of the anticoagulant.
Cholestyramine	2	Thyroid hormones (levothyroxine, liothyronine, liotrix, thyroid)	Cholestyramine may decrease the GI absorption of thyroid hormones by binding to them, resulting in lower systemic levels of thyroid hormones.
Cholestyramine	2	Valproic acid (divalproex sodium, valproic acid)	Cholestyramine may decrease the GI absorption of valproic acid, resulting in lower systemic levels of valproic acid.
Colesevelam	2	Glyburide	Colesevelam may decrease systemic levels of glyburide, decreasing the effect of glyburide.
Colesevelam	2	Levothyroxine	Colesevelam may decrease systemic levels of levothyroxine, decreasing the effect of levothyroxine.
Colesevelam	2	Oral contraceptives containing ethinyl estradiol and norethindrone	Colesevelam may decrease systemic levels of ethinyl estradiol and norethindrone, leading to lower systemic levels of hormone and potentially decreasing efficacy.

Significance Level 2=moderate severity

VI. Adverse Drug Events

The most common adverse reactions reported with the bile acid sequestrants are noted in Table 6. The adverse effect profiles of the bile acid sequestrants are similar; gastrointestinal side effects are the primary complaint for all agents.[7] Constipation and flatulence are also reported frequently.[3-5] These symptoms may diminish over time or may be relieved by increasing dietary fiber. All the bile acid sequestrants can cause an increase in triglyceride levels, and therefore should not be utilized in patients with triglyceride levels >400 mg/dL.[2] Cholestyramine and colestipol can decrease plasma folate levels, so supplementation should be considered in younger women and children.[2-4] In addition, bile acid sequestrants can decrease the absorption of vitamins A, D, E, K.[2-5]

Table 6. Adverse Drug Events (%) Reported with the Bile Acid Sequestrants [2-5]

Adverse Event(s)	Cholestyramine	Colesevelam	Colestipol
Body as a Whole			
Accidental injury	-	4	-
Asthenia/weakness	-	4	✔
Back pain	-	3	✔
Fatigue	-	-	✔
Flu syndrome	-	3	-
Infection	-	10	-
Pain	-	5	-
Rash	✔	-	✔
Swelling of hands and feet	-	-	✔
Vitamin A deficiency	✔	-	-
Vitamin D deficiency	✔	-	-
Cardiovascular			
Angina	-	-	✔
Chest pain	-	-	✔
Tachycardia	-	-	✔
Central Nervous System			
Dizziness/light-headedness	✔	-	✔
Headache	✔	6	✔
Insomnia	-	-	✔
Migraine	-	-	✔
Sinus headache	-	-	✔
Gastrointestinal			
Abdominal pain/discomfort	✔	5	✔
Anorexia	✔	-	✔
Constipation	✔	11	✔
Diarrhea	✔	5	✔
Dyspepsia	-	8	✔
Eructation	✔	-	-
Flatulence	✔	12	✔
Nausea	✔	4	✔
Steatorrhea	✔	-	-
Vomiting	✔	-	-
Hematological			
Hypoprothrombinemia associated with vitamin K deficiency	✔	-	-
Musculoskeletal			
Myalgia	-	2	✔
Osteoporosis	✔	-	-
Respiratory			
Cough increased	-	2	-
Pharyngitis	-	3	-
Rhinitis	-	3	-
Shortness of breath	-	-	✔
Sinusitis	-	2	-
Laboratory Test Abnormalities			
Abnormal liver function tests (AST, ALT, Alk Phos)	✔	-	✔
Changes in triglyceride levels	✔	✔	✔

Alk Phos=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase
- Event not reported or incidence <1%
✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the bile acid sequestrants are summarized in Table 7.

Table 7. Dosing and Administration for the Bile Acid Sequestrants[2-5]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Cholestyramine	Primary Hyperlipidemia: Initial: 4 g (1 packet or scoopful) once or twice a day Maintenance: 8-16 g (2-4 packets or scoopfuls) daily divided into 2 doses; maximum, 24 g daily Pruritus Associated With Partial Biliary Obstruction: Initial: 4 g (1 packet or scoopful) once or twice a day Maintenance: 8-16 g (2-4 packets or scoopfuls) daily divided into 2 doses; maximum, 24 g daily	Although an optimal dosage schedule has not been established, standard texts list a usual pediatric dose of 240 mg/kg/day in 2-3 divided doses, normally not to exceed 8 g/day.[4] The effects of long-term administration, as well as its effect in maintaining lowered cholesterol levels in pediatric patients are unknown.	Powder bulk: Regular (with sucrose), 4 g Light (with aspartame), 4 g Powder packets: Regular (with sucrose), 4 g Light (with aspartame), 4 g
Colesevelam	Primary Hyperlipidemia: Maintenance: 3 tablets twice per day with meals or 6 tablets once daily with a meal and liquid Type 2 Diabetes Mellitus: Maintenance: 3 tablets twice per day with meals or 6 tablets once daily with a meal and liquid	Safety and efficacy in children have not been established.	Tablet: 625 mg
Colestipol	Primary Hyperlipidemia: Tablets: Initial, 2 g once or twice daily Maintenance, 2-16 g/day once or in divided doses Granules: Initial, 5 g (1 packet or level teaspoon) once or twice daily Maintenance, 5-30 g (1-6 packets or level scoopfuls) given once or in divided doses	Safety and efficacy in children have not been established.	Granules for solution bulk: 5 g Granules for solution packet: 5 g 7.5 g Tablet: 1 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the bile acid sequestrants are summarized in Table 8.

Table 8. Comparative Clinical Trials Using the Bile Acid Sequestrants

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia				
Rosenson et al[16] Colesevelam 1.5-3.75 g/day vs placebo	DB, MC, PC, RCT Hypercholesterolemia patients, LDL-C >160 mg/dL, average age of 56 years old	N=137 6 weeks	Primary: LDL particle size and LDL particle number Secondary: Not reported	Primary: Mean LDL particle size increased significantly in the group receiving colesevelam 3.75 g/day (*P*=0.01). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.75 g/day by 13.7% (*P*=0.0002). Mean LDL particle number decreased significantly in the group receiving colesevelam 3.0 g/day by 6.8% (*P*=0.03). Secondary: Not reported
Bays et al[17] Colesevelam 3.75 g/day vs placebo	MA of 3 trials (each DB, MC, PC, PG, RCT) Patients were 18 years old or older and had an LDL-C ≥100 mg/dL and ≤250 mg/dL, TG ≤300 mg/dL and on stable doses of statin therapy, either atorvastatin, pravastatin or simvastatin for ≥4 weeks	N=204 6 weeks	Primary: Mean percent change in LDL-C level from baseline to end point Secondary: HsCRP, absolute and percent change in HDL-C, TC, apo AI, apo B, TG, and absolute change in hsCRP; safety (measured by incidence of treatment-emergent adverse events)	Primary: Patients receiving colesevelam with a statin had significantly greater reductions in LDL-C than those receiving placebo plus a statin at the end of the study (*P*<0.01 for absolute difference; *P*≤0.001 for % treatment difference). Secondary: HsCRP levels decreased significantly as compared to placebo when colesevelam was combined with simvastatin or pravastatin (*P*=0.0154 and *P*=0.0279, respectively). Patients receiving colesevelam with a statin did not have a significant increase in HDL-C as compared to those receiving placebo plus a statin at the end of the study (*P*>0.05). Patients receiving colesevelam with a statin had significantly greater reductions in TC than those receiving placebo plus a statin at the end of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the study (P<0.05). Apo B levels were not significantly different (P value not reported). No serious drug-related adverse events were reported. The incidence of drug-related adverse events was higher in the groups receiving colesevelam with a statin (13% to 26%) than placebo with a statin (0% to 13%; P value not reported).
The Lipid Research Clinics Coronary Primary Prevention Trial[18,19] Cholestyramine vs placebo	DB, MC, RCT Asymptomatic males with primary hypercholesterolemia, following a moderate cholesterol-lowering diet	N=3,806 7.4 years average	Primary: CHD death and/or nonfatal MI Secondary: TC and LDL-C changes, incidence rates of: positive stress tests, angina, coronary bypass surgery	Primary: The cholestyramine group had a 19% reduction in risk of CHD death or nonfatal MI (P<0.05). Secondary The cholestyramine group had a reduction in TC of 13.4% and a reduction in LDL-C of 20.3%. The placebo group had a TC reduction of 4.9% and a LDL reduction of 7.7% (P values not reported). Incidence rates of positive stress tests, angina and coronary bypass surgery were decreased in the cholestyramine group by 25%, 20%, and 21%, respectively (P values not reported).
Ballantyne et al[20] Rosuvastatin 80 mg vs rosuvastatin 80 mg and cholestyramine 16 g	MC, OL, PG, RCT Adults, 18 years and older, with severe hypercholesterolemia (LDL-C 190-400 mg/dL) and fasting TG <400 mg/dL	N=147 12 weeks (6 weeks of 40 mg rosuvastatin, followed by 6 weeks of rosuvastatin 80 mg with or without cholestryramine)	Primary: Percent change in LDL-C from baseline to end of treatment Secondary Percent change from baseline in LDL-C after 6 weeks of 40 mg rosuvastatin; percent change from baseline at 6 and 12 weeks of	Primary: At 12 weeks, no significant difference between the groups was seen: the rosuvastatin group had an LDL-C reduction of 56.4% and rosuvastatin with cholestyramine group had an LDL-C reduction of 60.5% (P<0.08). Secondary: LDL-C reductions were 52.2% after treatment with 40 mg rosuvastatin. Other measurements, TC, HDL-C, TG, apo B, apo AI and lipid ratios were not significantly different between the groups (P=0.20, 0.71, 0.47, 0.75, 0.53, 0.17, respectively). Decreases in CRP were 29% after 6 weeks, 42% after rosuvastatin 80 mg and 48% after rosuvastatin 80 mg with cholestryramine (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			rosuvastatin treatment for: TC, HDL-C, TG, apo AI, apo B, lipid ratios (LDL:HDL) and inflammatory markers (CRP, IL6); compliance	49% of patients in the cholestyramine group were not compliant with the cholestyramine treatment.
Eriksson et al[21] Cholestyramine 16 g vs cholestyramine 8 g and pravastatin 20 mg vs pravastatin 20 mg vs pravastatin 40 mg	MC, RCT Men and women, aged 30-65 years old	N=2,036 12 months	Primary: Reduction in LDL-C Secondary: Compliance	Primary: Percent change (CI) in LDL-C from baseline to end point within each group: Cholestyramine: –26% (–23% to –29%) Cholestyramine and pravastatin: –36% (–33% to –39%) Pravastatin 20 mg: –27% (–25% to –29%) Pravastatin 40 mg: –32% (–30% to –34%) Secondary: Compliance rates: Cholestyramine: 44% Cholestyramine and pravastatin: 53% Pravastatin 20 mg: 76% Pravastatin 40 mg: 78% Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common in the cholestyramine group and the cholestyramine with pravastatin group.
Insull et al[22] Colesevelam 2.3 g vs colesevelam 3.0 g vs	DB, MC, PC, RCT Patients with primary hypercholesterolemia, LDL-C levels between 130-220 mg/dL	N=467 32 weeks (8 weeks diet lead in and 24 weeks treatment)	Primary: Mean absolute change in LDL-C from baseline to the end of 24-week treatment Secondary: Mean percent change in LDL-C,	Primary: All doses of colesevelam resulted in significant absolute and percent change decreases in LDL-C at the end point as compared to placebo (P<0.001 for all). Absolute change decreases and percent decreases in LDL-C for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 14 mg/dL (9%), 19 mg/dL (12%), 24 mg/dL (15%) and 28 mg/dL (18%). Secondary: All doses of colesevelam resulted in significant reductions of TC (P<0.001). Absolute change decreases and percent decreases in TC for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
colesevelam 3.8 g vs colesevelam 4.5 g vs placebo			mean absolute and percent change in TC, apo B, apo AI, and median absolute change and percent change in HDL-C and TG	the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 10 mg/dL (4%), 15 mg/dL (6%), 18 mg/dL (7%) and 24 mg/dL (10%). All doses of colesevelam resulted in significant increases in HDL-C (P<0.001). Absolute changes (increases) and percent increases in TC for the 2.3 g, 3.0 g, 3.8 g, and 4.5 g doses were 2 mg/dL (3%), 2 mg/dL (4%), 2 mg/dL (3%) and 2 mg/dL (3%). All doses of colesevelam resulted in significant reductions in apo B relative to baseline (P<0.001). Changes in apo AI and lipoprotein did not result in significant changes relative to baseline, except the 2.3 g and 3.0 g doses resulted in significant changes in apo AI (P=0.02 and 0.03, respectively) TG levels did not change significantly as compared to placebo, however increases, 5% to 10%, were seen within groups from baseline to end point (P<0.05).
Hunninghake et al[23] Colesevelam 3.8 g vs atorvastatin 10 mg vs colesevelam 3.8 g and atorvastatin 10 mg vs atorvastatin 80 mg vs	DB, MC, PC, RCT Patients with elevated LDL-C levels ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change in LDL-C Secondary: Change in TC, HDL-C, TG, apo B, apo AI and lipoprotein(a) from baseline	Primary: All treatment groups resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions were –12% in the colesevelam 3.8 g group, –38% in the atorvastatin 10 mg group, –48% in the colesevelam 3.8 g and atorvastatin 10 mg group and –53% for the atorvastatin 80 mg group (P<0.05, P<0.0001, P<0.0001, and P<0.0001, respectively, for change from baseline to end point). Secondary: Colesevelam 3.8 g/day reduced TC –6% (P<0.05), increased HDL-C 3% (P<0.05), and increased TG 10% (P value not reported). Atorvastatin 10 mg reduced TC –27% (P<0.0001), increased HDL-C 8% (P<0.05), and reduced TG –24% (P<0.05). Colesevelam 3.8 g and atorvastatin 10 mg reduced TC –31%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				(*P*<0.0001), increased HDL-C 11% (*P*<0.05), and reduced TG –1% (*P* value not reported). Atorvastatin 80 mg reduced TC –39% (*P*<0.0001), increased HDL-C 5% (*P*<0.05), and reduced TG –33% (*P*<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam 3.8 g with atorvastatin 10 mg. No significant differences in HDL-C were found between the groups (*P* value not reported). Apo B levels decreased significantly for all groups relative to baseline (*P*<0.01). No significant changes in Apo AI and lipoprotein were reported.
Knapp et al[24] Colesevelam 3.8 g vs simvastatin 10 mg vs colesevelam 3.8 g with simvastatin 10 mg vs colesevelam 2.3 g vs simvastatin 20 mg vs	DB, MC, PC, RCT Men and women, age 18 years and older, with elevated LDL-C levels, ≥160 mg/dL and TG ≤300 mg/dL and not taking cholesterol-lowering medication	N=258 6 weeks	Primary: Change in serum LDL-C from baseline to end point Secondary: Percent change in LDL-C, mean and percent change in TC, HDL-C, TG, apo B and apo AI from baseline	Primary: LDL-C serum changes were –7 mg/dL in the placebo group, –31 mg/dL in the colesevelam 3.8 g group, –48 mg/dL in the simvastatin 10 mg group –80 mg/dL in the colesevelam 3.8 g and simvastatin 10 mg group, –17 mg/dL in the colesevelam 2.3 g group, –61 mg/dL in the simvastatin 20 mg group and –80 mg/dL for the colesevelam 2.3 g and simvastatin 20 mg group (*P*<0.05, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, and *P*<0.0001, respectively, for change from baseline to end point). Secondary: LDL-C percent changes were –4% in the placebo group, –16% in the colesevelam 3.8 g group, –26% in the simvastatin 10 mg group, –42% in the colesevelam 3.8 g and simvastatin 10 mg group , –8% in the colesevelam 2.3 g group, –34% in the simvastatin 20 mg group and –42% for the colesevelam 2.3 g and simvastatin 20 mg group (*P*<0.05, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, *P*<0.0001, and *P*<0.0001, respectively, for change from baseline to end point). Significant changes from baseline were found for all treatment groups in mean and percent change in TC (*P*<0.0001 for all except colesevelam 2.3 g for which *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
colesevelam 2.3 g with simvastatin 20 mg vs placebo				Significant changes from baseline were found for mean and percent change in HDL-C for simvastatin 10 mg (P<0.05), colesevelam 3.8 g with simvastatin 10 mg (P<0.0001), colesevelam 2.3 g (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant changes from baseline were found for mean and percent change in TG for colesevelam 3.8 g (P<0.05), simvastatin 10 mg (P<0.05), simvastatin 20 mg (P<0.05), and colesevelam 2.3 g with simvastatin 20 mg (P<0.05). Significant reductions from baseline for apo B were found for all groups. Reductions were significant (P<0.05) compared to placebo for all treatment groups except colesevelam 2.3 g. Significant increases in apo AI were seen in all treatment groups except simvastatin 10 mg (P<0.05).
Davidson et al [25] Colesevelam 2.3 g vs lovastatin 10 mg vs colesevelam 2.3 g and lovastatin 10 mg taken together vs colesevelam 2.3 g and lovastatin 10 mg taken	DB, MC, PC, RCT Patients with elevated LDL-C levels	N=135 4 week	Primary: Percent change in LDL-C Secondary: Changes in TC, HDL-C, TG, apo B	Primary: Colesevelam 2.3 g and lovastatin 10 mg together significantly reduced LDL-C 34% (-60 mg/dL; P<0.0001). Colesevelam 2.3 g and lovastatin 10 mg apart significantly reduced LDL-C 32% (-53 mg/dL; P<0.0001). Lovastatin 10 mg reduced LDL-C 22% (-39 mg/dL; P value not reported). Colesevelam 2.3 g reduced LDL-C 7% (-13 mg/dL; P value not reported). Both combination treatments were more effective than either treatment alone (P<0.05). Secondary: Both combination treatments resulted in reductions in TC by 21% and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
apart vs placebo				apo B by 24% (P<0.0001 for each). No significant effect on HDL-C or TG was found for the combination treatments (P value not reported).
Type 2 Diabetes Mellitus				
Zieve et al[26] GLOWS Colesevelam 3.75 g/day vs placebo	DB, PC, PG, PRO, RCT Patients diagnosed with type 2 diabetes, an HbA_{1c} 7.0%-10.0%, and on a stable dose of a sulfonylurea and/or metformin as their only antidiabetic agent for ≥90 days	N=65 12 weeks	Primary: Change in HbA_{1c} from baseline Secondary: Changes in fructosamine levels, FPG levels, postprandial glucose level, meal glucose response (difference between pre and postprandial glucose levels) % change in lipids: LDL, TC, TG, apo AI and B	Primary: The change in HbA_{1c} from baseline to 12 weeks for the colesevelam group was –0.3% and for placebo +0.2%, for a treatment difference of 0.5% (P=0.007). For patients with a baseline HbA_{1c} ≥8.0, there was a greater difference in HbA_{1c}, –1.0%, after 12 weeks of treatment (P=0.002). The reduction in HbA_{1c} in the treatment groups did not differ based on oral antidiabetic treatment (P value not reported). Secondary: Significantly lower FPG was seen in the colesevelam group at weeks 4 and 8, (P=0.016, P=0.011), but not at week 12. Significantly lower fructosamine levels were seen in the colesevelam group at week 12 (P=0.011). Significantly lower postprandial glucose levels were seen in the colesevelam group at week 12 (P=0.026). No significant difference was seen in meal glucose response (P=0.195). Significantly lower lipid parameters, including LDL, TC, apo B and LDL particle concentration, were seen in the colesevelam group as compared to placebo (P=0.007, P=0.019, P=0.003, and P=0.037, respectively).

Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial
Miscellaneous abbreviations: apo=apolipoprotein, CHD=coronary heart disease, CRP=C-reactive protein, FPG=fasting plasma glucose, GLOWS=Glucose-Lowering Effect Of WelChol; HbA_{1c}=glycosylated hemoglobin, HDL=high-density lipoprotein, HDL-C=high-density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IL6=interleukin 6, LDL=low-density lipoprotein, LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, TC=total cholesterol, TG=triglycerides

IX. Conclusions

Included in the bile acid sequestrant class are cholestyramine, colesevelam and colestipol. The bile acid sequestrants are primarily indicated for the reduction of total cholesterol and low-density lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolemia.[2-5] These agents reduce cholesterol levels by binding to, and removing bile acid from circulation. The resultant lower levels of bile acid lead to increased breakdown of cholesterol into bile acid, lowering the overall total cholesterol levels.[6] The bile acid sequestrants are effective at reducing LDL-C, while slightly increasing high-density lipoprotein cholesterol.[7]

There is a lack of head-to-head trials comparing agents within the bile acid sequestrant class to each other and current treatment guidelines do not give preference to one agent over another.[7-10,12] Although colesevelam may offer a more favorable drug-interaction profile, potential drug interactions with bile acid sequestrants may be minimized by adjusting the timing of the doses. Cholestyramine and colestipol are available generically. Colesevelam and colestipol are available in tablet formulation. Colestipol is also available as granules for suspension. Cholestyramine is only available in a powder form for suspension.

Treatment guidelines recommend statin therapy as first-line treatment for dyslipidemia.[7-10,12] The guidelines recommend the use of bile acid sequestrants as an alternative for patients who have a contraindication or intolerance to a statin, or as additional treatment for patients who can not achieve goal cholesterol levels with monotherapy alone. All the bile acid sequestrants can be used in conjunction with a statin, or as monotherapy. Colesevelam recently received an FDA indication for the adjunctive treatment of type 2 diabetes; its use for improving glycemic control is not addressed in the current American Diabetes Association treatment guidelines.[5]

Clinical trials demonstrate efficacy of each agent in reducing low-density lipoprotein, non–high-density lipoprotein, total cholesterol and other markers of dyslipidemia.[16-26] The bile acid sequestrants are an effective alternative option to first-line treatment or as adjunctive treatment for decreasing cholesterol.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics in this class and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand bile acid sequestrant is recommended for preferred status. It is recommended that the following criteria for non-preferred products remain as currently listed below, but the length of authorization for non-preferred products be changed from lifetime to 3 years.

Questran®*

- The patient has had a documented intolerance to cholestyramine powder.

Questran Light®*

- The patient has had a documented intolerance to cholestyramine light powder.

Colestid®*

- The patient has had a documented intolerance to colestipol tablets or granules.

Welchol®

- If being prescribed for lipid reduction, the patient has had a documented side effect, allergy, or treatment failure to cholestyramine and colestipol.

OR

- If being prescribed for additional improved glycemic control, the patient must have been unable to obtain a satisfactory hemoglobin A1C reduction with metformin and one other oral anti-diabetic agent.

References

1. Cardiovascular drugs 24:00, Antilipemic agents 24:06, Bile acid sequestrants 24:06:04. In: McEvoy GK, editor; American Hospital Formulary Service. AHFS drug information 2007 [monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2007 [cited 2008 Mar 3]. Available from: http://online.statref.com.
2. Colestid® tablets [package insert]. New York (NY): Pfizer; 2006 Jun.
3. Colestid®, Flavored Colestid® for oral suspension [package insert on the Internet]. New York (NY): Pfizer; 2006 Jun [cited 2008 Mar 4]. Available from: http://www.pfizer.com/files/products/uspi_colestid_os.pdf.
4. Questran®, Questran Light® [package insert]. Spring Valley (NY): Par Pharmaceutical Companies, Inc; 2006 May.
5. WelChol® [package insert]. Parsippany (NJ): Sankyo Pharma, Inc; 2008 Jan.
6. Rosenson RS. Lipid lowering with drugs other than statins and fibrates: In: Rose BD, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2008 [cited 2008 Jan 25]. Available from: http://www.utdol.com/utd/index.do.
7. National Institutes of Health: National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report [guideline on the Internet]. Circulation. 2002 Dec 17 [cited 2007 Jan 26];106(25):3143-421. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm.
8. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [guideline on the Internet]. Circulation. 2004 Jul 13 [cited 2007 Jan 28];110(2):227-39. Available from: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3upd04.htm.
9. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al; American Heart Association; American College of Cardiology; National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute [guideline on the Internet]. Circulation. 2006 May 16 [cited 2007 Jan 28];113(19):2363-72. Available from: http://www.americanheart.org/presenter.jhtml?identifier=3004572.
10. Institute for Clinical Systems Improvement (ICSI). Healthcare guideline: lipid management in adults [guideline on the Internet]. 10th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2007 Jun [cited 2007 Dec 19]. Available from: http://www.icsi.org/lipid_management_3/lipid_management_in_adults_4.html.
11. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, et al; American Heart Association. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing [guideline on the Internet]. Circulation. 2007 [cited 2007 Jan 28];115(14):1948-67. Available from: http://www.americanheart.org/presenter.jhtml?identifier=3004597.
12. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil. 2007;14 Suppl 2:S1-113.
13. Heathcote EJ. Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines [serial on the Internet]. Hepatology. 2000 Apr [cited 2008 Mar 03];31(4):1005-13. Available from: https://www.aasld.org/eweb/docs/biliarycirrhosis.pdf.
14. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2007 [cited 2008 Jan 11]. Available from: http://www.thomsonhc.com/.
15. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2007 [cited 2008 Jan 11]. Available from: http://online.factsandcomparisons.com.

16. Rosenson RS. Colesevelam HCl reduces LDL particle number and increases LDL size in hypercholesterolemia. Atherosclerosis 2006;185:327-30.
17. Bays HE, Davidson M, Jones MR and Abby SL. Effects of colesevelam hydrochloride on low-density lipoprotein cholesterol and high-sensitivity c-reactive protein when added to statins in patients with hypercholesterolemia. Am J Cardiol. 2006 Apr 15;97(8):1198-205.
18. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease.I. JAMA. 1984 Jan 20;251(3):351-64.
19. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984 Jan 20;251(3):365-74.
20. Ballantyne C, Miller E, Chitra R. Efficacy and safety of rosuvastatin alone and in combination with cholestyramine in patients with severe hypercholesterolemia: a randomized, open-label, multicenter trial. Clin Ther. 2004 Nov;26(11):1855-64.
21. Eriksson M, Hådell K, Holme I, Walldius G, Kjellström T. Compliance with and efficacy of treatment with pravastatin and cholestyramine: a randomized study on lipid-lowering in primary care. J Intern Med. 1998 May;243(5):373-80.
22. Insull W Jr, Toth P, Mullican W, Hunninghake D, Burke S, Donovan JM, Davidson MH. Effectiveness of colesevelam hydrochloride in decreasing LDL cholesterol in patients with primary hypercholesterolemia: a 24-week randomized controlled trial. Mayo Clin Proc. 2001 Oct;76(10):971-82.
23. Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis. 2001 Oct;158(2):407-16.
24. Knapp HH, Schrott H, Ma P, Knopp R, Chin B, Gaziano JM, Donovan JM, Burke SK, Davidson MH. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med. 2001 Apr 1;110(5):352-60.
25. Davidson MH, Toth P, Weiss S, McKenney J, Hunninghake D, Isaacsohn J, Donovan JM, Burke SK. Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decreases low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. Clin Cardiol. 2001 Jun;24(6):467-74. ABSTRACT
26. Zieve FJ, Kalin MF, Schwartz S et al. Results of the Glucose-Lowering Effect of Welchol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. Clin Ther. 2007 Jan;29(1):74-83.